ENDOCRINE SOCIETY JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

J Clin Endocrinol Metab. 2018 May; 103(5): 1818–1826.
Published online 2018 Feb 22. doi: 10.1210/jc.2017-01196: 10.1210/jc.2017-01196

PMCID: PMC6276710
PMID: 29481662

A Common DIO2 Polymorphism and Alzheimer Disease Dementia in African and European Americans

Elizabeth A McAninch,[1] Kumar B Rajan,[2] Denis A Evans,[2] Sungro Jo,[1] Layal Chaker,[3] Robin P Peeters,[3] David A Bennett,[4] Deborah C Mash,[5] and Antonio C Bianco[1]

[1]Division of Endocrinology and Metabolism, Rush University Medical Center, Chicago, Illinois
[2]Department of Internal Medicine, Rush Institute for Healthy Aging, Rush University Medical Center, Chicago, Illinois
[3]Rotterdam Thyroid Center, Erasmus University Medical Center, Rotterdam, The Netherlands
[4]Department of Neurologic Sciences, Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, Illinois
[5]Department of Neurologic Sciences, University of Miami Miller School of Medicine, Miami, Florida

Correspondence and Reprint Requests: Antonio C. Bianco, MD, PhD, Section of Endocrinology, Diabetes & Metabolism, University of Chicago Medical Center, 5841 South Maryland Avenue, MC1027, Room M267, Chicago, Illinois 60637. E-mail: abianco@deiodinase.org.

Received 2017 May 24; Accepted 2018 Feb 16.

Copyright © 2018 Endocrine Society

Abstract

Context

A common single nucleotide polymorphism in *DIO2*, Thr92AlaD2, has been associated with a transcriptome typically found in neurodegenerative diseases in postmortem human brain tissue.

Objective

To determine whether Thr92AlaD2 is associated with incident Alzheimer disease (AD).

Design

Population-based study; human brain tissue microarray.

Setting

Community-based cohorts from Chicago and northeastern Illinois and religious clergymen from across the United States constituted the primary population. A representative sample of the U.S. population was used for secondary analyses.

Participants

3054 African Americans (AAs) and 9304 European Americans (EAs).

Main Outcome Measure

Incident AD.

Results

In the primary population, AAs with Thr92AlaD2 had 1.3 times [95% confidence interval (CI), 1.02 to 1.68; $P = 0.048$] greater odds of developing AD. AAs from a second population with Thr92AlaD2 showed a trend toward increased odds of dementia (odds ratio, 1.33; 95% CI, 0.99 to 1.78; $P = 0.06$) and 1.35 times greater odds of developing cognitive impairment not demented (CIND; 95% CI, 1.09 to 1.67; $P = 0.006$). Meta-analysis showed that AAs with Thr92AlaD2 had 1.3 times increased odds of developing AD/dementia (95% CI, 1.07 to 1.58; $P = 0.008$). In EAs, no association was found between Thr92AlaD2 and AD, dementia, or CIND. Microarray of AA brain tissue identified transcriptional patterns linked to AD pathogenesis.

Conclusions

Thr92AlaD2 was associated with molecular markers known to underlie AD pathogenesis in AAs, translating to an observed phenotype of increased odds of developing AD/dementia in AAs in these populations. Thr92AlaD2 might represent one factor contributing to racial discrepancies in incident AD.

The present study evaluated populations with longitudinal cognitive outcomes and found Thr92AlaD2 to be associated with incident Alzheimer disease in African Americans but not European Americans.

The type II deiodinase (D2) activates thyroxine (T4) to triiodothyronine (T3) in peripheral tissues, including the cerebral cortex, where it is highly expressed (1). A common single nucleotide polymorphism (SNP), rs225014, is present in *DIO2* with a minor-allele frequency (MAF) of ~40% (2). This SNP results in a single amino acid substitution of threonine (Thr) for alanine (Ala) at position 92 in the D2 protein (Thr92AlaD2) (3). The substitution is distant from D2's catalytic site, within the instability loop (4). However, the effect of this polymorphism on D2 activity has been not been consistently replicated. Some studies have suggested that Thr92AlaD2

kinetics are largely intact when transiently expressed in cells (2) and that carriers: (1) exhibit normal markers of T3 responsiveness in brain tissue (5); (2) have normal thyroid function test results (2, 6, 7); and (3) require equivalent replacement doses of levothyroxine in hypothyroidism (8, 9). However, other studies have suggested that Thr92AlaD2 does impair T4-to-T3 conversion *in vitro* and *in vivo* (10).

The clinical relevance of Thr92AlaD2 has been controversial, because it has been associated with diverse metabolic and cognitive phenotypes (11). These associations have not been consistently replicated. Thus, although this could have resulted from multiple pathway mechanisms or other gene-to-gene interactions (12), study design heterogeneity and the lack of statistical power have likely contributed to the poor reproducibility and made these studies prone to false-positive results (11). At least some of the molecular consequences of Thr92AlaD2 expression have been described. Thr92AlaD2 accumulates in cells (5, 10) and, when stably expressed, instead of remaining in the endoplasmic reticulum, escapes to the Golgi apparatus, which exhibits a perturbed morphology (5). Human temporal lobe samples from Thr92AlaD2 carriers exhibit transcriptional alterations in processes typically associated with neurodegenerative diseases, such as amyloid-beta (Aβ) peptide processing (5).

In the present study, we tested the hypothesis that carriers of the Thr92AlaD2 polymorphism have an increased risk of incident Alzheimer disease (AD). Although this locus has not been identified in previous genome-wide association studies (13–15), the candidate gene approach could still identify a moderate association that would provide novel insight into the multifactorial pathogenesis of AD (16, 17). The epidemiology and tissue pathology of AD vary by ethnicity, with a greater incidence and prevalence of AD in African Americans (AAs) compared with European Americans (EAs) (18). Also, AAs are more likely to have mixed tissue pathologic features compared with clinically matched EAs (19). Thus, well-described populations with AA and EA participants from longitudinal, population-based studies with cognitive outcomes and SNP availability were used.

Subjects and Methods

Study populations and design

Three well-described, longitudinal studies, the Chicago Health and Aging Project (CHAP) (20), the Religious Orders Study (ROS) (21), and the Rush Memory and Aging Project (MAP) (22, 23), which had used nearly identical methods for clinical diagnosis of AD, were used for the primary investigations.

CHAP has been described previously (20). In brief, residents from a geographically defined, biracial community of AA and EA participants in Chicago from 1993 to 2012 were enrolled. Interviews, including cognitive testing, were performed in ~3-year cycles for 18 years; genotype data were available for 3656 participants (24).

The ROS began in 1994 and enrolled older Catholic priests, nuns, and brothers from groups

31/10/2023,

across the United States (21). MAP started in 1997, enrolling older community-based individuals from retirement communities, other housing units, and social service agencies and church groups in northeastern Illinois (22, 23). In ROS and MAP, participants without known dementia were enrolled and underwent annual clinical evaluations; SNP data were available from 1707 ROS and MAP participants.

For replication of the main findings, another large, homogenous cohort with the same outcome measures was not identified. Data from a large, biracial cohort are available but the cohort was a composite from >10 smaller, relatively heterogeneous studies (14). Thus, the Health and Retirement Study (HRS) was used as a secondary population. HRS is a longitudinal survey of a representative sample of the U.S. population aged >50 years occurring every 2 years (25). Publically available demographic data, cognitive outcomes, and genotyping data for 6995 participants were obtained through the National Institutes of Health Database of Genotypes and Phenotypes (26).

Cognitive function and AD diagnosis

A composite cognitive function score for CHAP was generated from the results of four cognitive tests for episodic memory, executive functioning, and the Mini-Mental State Examination (MMSE) by averaging the test results together after centering and scaling each to their baseline mean and standard deviation. In a stratified random sample, CHAP participants underwent a uniform clinical evaluation within their homes that included a structured medical history, neurologic examination, and cognitive assessment consisting of a battery of 19 tests for episodic memory, executive function, general orientation, and global cognition (27). A neurologist, who was unaware of previously collected data, reviewed the results and diagnosed mild cognitive impairment (MCI) and AD according to the National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria. These criteria require a history of cognitive decline and evidence of impairment in two or more cognitive domains, one of which must be memory, for a diagnosis of AD.

In the ROS/MAP, clinical evaluations were performed during annual home visits. A similar cognitive function test score was created for ROS/MAP with a comprehensive battery of tests for episodic memory, executive functioning, verbal fluency, and visual-spatial tests for cognition. The clinical diagnoses of MCI and AD were determined with the same methodology as in CHAP (28).

In HRS, a neuropsychological test battery was administered, and the results were reviewed by a geropsychiatrist, neurologist, neuropsychologist, and cognitive neuroscientist, who assigned a preliminary research diagnosis determined from the composite memory test scores ranging from 0 to 27. The composite score included immediate and delayed recall items, the serial sevens (counting backward from 100 by seven), and backward counting (29). The diagnoses were within three categories: normal cognitive function (score, 12 to 27), cognitive impairment not demented (CIND; score, 7 to 11), and dementia (score, 0 to 6). Data on functional impairment was reported by the participant or informant and incorporated into the assessment (29) in accordance with reported criteria including the Diagnostic and Statistical Manual of Mental

Disorders III-revised and IV (25). HRS participants with dementia were not further stratified by etiology (*e.g.,* AD or vascular).

The different diagnostic strategies used in CHAP/ROS/MAP and HRS deserve emphasis. Although in CHAP/ROS/MAP, clinical diagnoses of MCI and AD were determined, the HRS participants with abnormal cognitive function were categorized as either having CIND or nonspecific dementia. CHAP exhibited a greater AD prevalence estimate than did HRS owing to the higher threshold for dementia diagnosis used in HRS (30). Thus, it is possible that CIND participants in HRS would have had a diagnosis of AD in the CHAP or ROS/MAP (30). In our analyses, we initially assessed for incident dementia in HRS but then expanded our approach to assess for an association at the milder cognitive phenotypes (MCI and CIND), because this was thought to better capture any genotype-phenotype association.

Genotyping of DIO2 rs225014

In CHAP, genotyping was performed using the hME Sequenom MassARRAY platform (Agena Bioscience) (24). In ROS/MAP, genotyping data were generated using an Affymetrix 6.0 platform (Thermo Fisher Scientific) (31). Both CHAP and ROS/MAP data were imputed using a multiethnic reference population in 1000 Genome, pilot 1, version 2, reference data in the same quality control pipeline. The overall imputation quality score was >0.98 for rs225014. In HRS, SNPs were identified using the Illumina beadchip platform and rs225014 genotype status imputed based on the 1000 Genomes Project (32).

Covariates

All our regression models were adjusted for age (centered at 75 years), sex, and education (measured in number of years of schooling completed, centered at 12 years).

Statistical analysis

Descriptive analysis was performed using the mean and standard deviation for continuous measures and percentages for categorical measures. Our initial descriptive analysis was stratified by race for each of the study populations. Descriptive comparisons were made using a two-sample t test for continuous measures and χ^2 test statistic for categorical measures. The main objective of the present investigation was to examine the association of Thr92AlaD2 genotype status with diagnosis of AD. The HRS classification of dementia was determined using the memory test score (score 0 to 6), and the cutoff scores provide the prevalence of dementia in HRS rather than the time-at-incidence of dementia. The CHAP study also included incident AD diagnosis in 3-year intervals, leading to a right-censored time of diagnosis. For these reasons, we used a logistic regression model after adjusting for age, sex, education, and self-reported hypertension and diabetes (27).

To understand the association of the Thr92AlaD2 polymorphism with AD, we used three differ-

ent modeling approaches: an additive model was used to determine whether the presence of each Ala allele was associated with increased odds of AD; a dominant model was used to compare participants with at least one copy of the Ala allele vs those homozygous for the Thr allele; and a recessive model was used to determine whether those homozygous for the Ala allele had an increased odds of AD compared with those with at least one copy of the Thr allele. The reasons for the various approaches were to determine whether the association of the polymorphism could be understood with greater detail. After population-specific estimates of the association between the Thr92AlaD2 polymorphism and AD/dementia, a meta-analysis of odds ratios (ORs) was performed using an inverse variance weighted estimation method in a fixed effects model (two AA studies and three EA studies was not enough to fit a random or mixed effects meta-analysis model) using metafor package in the R program.

Linkage disequilibrium

Regional linkage disequilibrium (LD) plots were generated using the SNP Annotation and Proxy Search tool (Broad Institute) (33) based on genotype data from the 1000 Genomes Project. Plots were created for rs225014 with data from CEU (Utah residents with Northern and Western European ancestry) and YRI (Yoruba in Ibadan, Nigeria) backgrounds (Fig. 1).

Microarray analysis

The University of Miami Brain Endowment Bank provided genomic DNA and brain tissue samples from postmortem human donors, just as in previous studies; genotyping of genomic DNA had been performed according to previously reported methods (5). AA brain samples from 11 donors without known thyroid or neurologic disease (4 with Thr/Thr, 4 with Thr/Ala, and 3 with Ala/Ala) were matched by age ($P = 0.54$), male sex, and body mass index (BMI) ($P = 0.82$) and chosen for further studies. Homogenous samples were dissected from Brodmann area 38 (temporal cortex) by a neuroanatomist. The samples were processed and microarray was performed as previously reported (5). Affymetrix Transcriptome Analysis Console software (Thermo Fisher Scientific) was used to identify individual genes that demonstrate substantial differential expression in the comparison of Ala/Ala vs Thr/Thr samples from AA donors (Supplemental Fig. 1). A differential expression analysis was also performed for data obtained in the previous microarray of structurally identical EA samples (Ala/Ala, n = 6 vs Thr/Thr, n = 6). Those transcripts exhibiting differential expression (3253 from AA samples and 1676 from EA samples) were then assessed via Pathway Analysis software (Ingenuity).

Institutional review board approval

The Rush University Medical Center institutional review board (IRB) approved the CHAP and ROS/MAP studies. The University of Michigan IRB approved the HRS study. The University of Miami Brain Endowment Bank provided genomic DNA and brain tissue samples; their protocols were also IRB approved. HRS data were obtained from the database of Genotypes and Phenotypes with Rush IRB approval. All participants provided written informed consent.

Results

In the primary study populations, AAs were younger, had a greater BMI, had a lower level of education, were more likely to have a hemoglobin A1c level >6.5%, and exhibited less mortality during the period of observation compared with EAs (Table 1). The ROS/MAP participants were older than the CHAP participants, were more likely to be female, had higher levels of education, and experienced greater mortality. HRS participants were younger, more likely to have diabetes, and had less mortality than those from the primary study populations (Table 1). Fewer AAs had available cognitive and genotype data in HRS (n = 733) than in CHAP (n = 2321).

Genotyping of the CHAP AA participants revealed the MAF to be 45.3% (Table 1). In the EA participants from CHAP and ROS/MAP, rs225014 MAF was 35.7% and 34.5%, respectively. The racial discrepancy in MAF was similar in HRS. When all the participants from CHAP, ROS/MAP, and HRS were combined and stratified by race, the MAF in the AAs was significantly greater than that in the EAs (43.9% vs 36.5%; $P < 0.001$; Supplemental Table 1). No deviation from Hardy-Weinberg equilibrium was found in either racial group.

Additive, dominant, and recessive statistical models were used to assess for an association between the Thr92AlaD2 genotype and AD (Table 2). CHAP AAs with the Thr92AlaD2 polymorphism had 1.31 times greater odds of AD [95% confidence interval (CI), 1.02 to 1.68; $P = 0.048$] than those without the polymorphism (additive model). With the dominant model, they had 1.85 times greater odds of AD (95% CI, 1.20 to 2.85; $P = 0.005$). In the AAs from HRS with the Thr92AlaD2 polymorphism, a trend was seen toward increased odds of dementia (additive model OR, 1.33; 95% CI, 0.99 to 1.78; $P = 0.06$; dominant model OR, 1.14; 95% CI, 0.75 to 1.73; $P = 0.54$). A meta-analysis showed that AAs with the Thr92AlaD2 polymorphism had greater odds of AD/dementia (additive model OR, 1.30; 95% CI, 1.07 to 1.58; $P = 0.008$; dominant model OR, 1.60; 95% CI, 1.15 to 2.22; $P = 0.006$). In the EA participants, no association was found between the rs225014 genotype and AD/dementia in CHAP, ROS/MAP, or HRS.

We found major differences in AD/dementia diagnostic strategies between the primary study populations and HRS [*i.e.,* the clinical diagnosis of AD (CHAP/ROS/MAP) vs unspecified dementia categorization (HRS); and the higher threshold for the dementia diagnosis in HRS than for AD in CHAP/ROS/MAP] (30). Therefore, we broadened our scope to assess for an association at milder degrees of cognitive impairment (Table 3). In AAs from HRS with Thr92AlaD2, the odds of developing CIND was increased 1.35 times in the additive model (95% CI, 1.09 to 1.67; $P = 0.006$); this trend was preserved in the dominant model (OR, 1.35; 95% CI, 0.99 to 1.84; $P = 0.06$). CHAP AAs with Thr92AlaD2 did not exhibit increased odds of developing MCI. In the EA participants, no association was found between rs225014 genotype and MCI/CIND in any of the populations.

Thr92AlaD2 genotype status was not associated with BMI or diabetes in the primary study populations (Table 4). Serum T4 levels were only available for some of the CHAP participants; however, no association was found between Thr92AlaD2 genotype status and serum T4 level. Also, no association was found between Thr92AlaD2 genotype status and mortality.

Genetic regional LD plots of SNPs near rs225014 for persons of African (Fig. 1A) vs European (Fig. 1B) descent showed substantial differences in haploblock inheritance patterns. Although the EA population had many SNPs with high LD ($r^2 > 0.6$) with rs225014 within the region, the AA population had only one SNP (rs225015) in high LD ($r^2 = 0.93$), with rs225014. This indicates that the allelic inheritance patterns in the chromosomal region near rs225014 differ greatly between these racial ethnic groups.

Brain samples were selected from male AA donors matched by age and BMI, and microarray was performed as previously reported (5). Differential expression analysis of the microarray data from AA samples revealed 3253 substantially differentially expressed transcripts in the comparison of Ala/Ala (n = 3) vs Thr/Thr (n = 4). Next, these 3253 transcripts were run through pathway analysis software that (1) identified the cascade of upstream transcriptional regulators that could explain these observed gene expression changes; and (2) predicted for diseases associated with the observed expression patterns. A total of 107 upstream regulators were statistically significant (Supplemental Table 2), including amyloid precursor protein (APP) ($P = 0.0007$), microtubule-associated protein tau ($P = 0.005$), and presenilin 1 ($P = 0.02$), all important in AD pathogenesis. In the predicted disease function of pathway analysis, evidence was found of neurologic disease (Supplemental Table 3), specifically AD ($P = 0.008$), neurodegeneration ($P = 0.009$), and tauopathy ($P = 0.002$; Supplemental Table 4).

From the previous EA microarray data (5), a new analysis was performed. A total of 1676 transcripts were significantly differentially expressed in the comparison of Ala/Ala (n = 6) and Thr/Thr (n = 6) samples. We found 110 important upstream regulators (Supplemental Table 5); this did not identify molecules known to be central in the pathogenesis of AD (APP, microtubule-associated protein tau, and presenilin 1; P = NS). Pathway analysis of differentially expressed genes also did not reveal any neurodegenerative diseases to be substantial (Supplemental Table 6).

Discussion

The Thr92AlaD2 polymorphism, more prevalent in AAs than in EAs, is associated with the development of AD in AAs, but not EAs, in our study populations. A major strength of our studies was the use of large, well-characterized populations containing both AA and EA participants, in addition to a complimentary molecular analysis of both AA and EA brain samples. Although design differences were present among the population studies that made direct comparisons challenging [*i.e.*, the higher threshold for dementia diagnosis in HRS than for AD in CHAP/ROS/MAP (30); the nonspecific dementia classification of HRS participants vs the clinical diagnosis of AD in CHAP/ROS/MAP; and the smaller AA sample size of HRS compared with CHAP], we addressed this by assessing not only for incident AD/dementia but also for incident MCI/CIND. That our findings were consistent among their racial stratifications across these different populations is reassuring; however, further studies of AA populations using a specific clinical diagnosis of AD are warranted to replicate our findings. Our findings support the hypothesis that Thr92AlaD2 is a risk factor for neurodegenerative disease in AAs and that Thr92AlaD2 might represent one factor contributing to racial discrepancies in incident AD. This locus might not have been identified

in a previous genome-wide association study with AA participants (14) because of its moderate effect size (16, 17).

Although the mechanistic explanation for these findings is not implicit, human brain tissue from EA, and now AA, donors with the Thr92AlaD2 risk allele exhibited transcriptional patterns associated with neurodegenerative diseases (5). Thr92AlaD2 has been documented *in vitro* to be ectopically located in the Golgi apparatus that exhibits an abnormal morphology with disruption of the expression of many Golgi-related transcripts; the resulting cellular messenger RNA profile is enriched in transcripts altered in diseases with abnormal Aβ processing (5). Altered Golgi trafficking of APP has been implicated in development of AD, because Aβ peptide accumulation causes Golgi structural defects that further affect APP trafficking and processing (34). Thus, it is conceivable that the cellular and Golgi perturbation associated with Thr92AlaD2 expression promote dysfunction in pathways involved in Aβ peptide processing and contribute to development of AD. It remains possible that as yet unidentified causal markers could contribute to the racially dependent phenotype.

To the best of our knowledge, ours is the first study to find a Thr92AlaD2-associated phenotype that differs by race, although previous studies of this SNP have been heavily weighted toward Caucasian racial ethnic groups. For instance, in a previous study of nondemented elderly Caucasians, Thr92AlaD2 was not associated with early imaging markers of AD (6).

Understanding the mechanism underlying this association is particularly important in the context of prevention. Mitochondrial dysfunction and Aβ accumulation likely contribute to oxidative stress in AD, and cross-sectional data have suggested improved cognitive performance among those with higher antioxidant intake, although interventional trials have not consistently demonstrated protection (35). Mitochondrial dysfunction and oxidative stress markers were present in the transcriptomes of human temporal pole samples from Thr92AlaD2 carriers and in the cell model of Thr92AlaD2 expression; some of these alterations in Thr92AlaD2-expressing cells were reversed with antioxidant treatment (5). Future studies are needed to determine whether antioxidants have a role in the prevention of AD among AA Thr92AlaD2 carriers.

In previous studies of Brazilian (36), EA (3), Pima Indian (37), Danish (38), and Amish (39) populations, the rs225014 MAF was ~40%. In our biracial population, the MAF was greater in the AA than in the EA participants. This finding requires confirmation in other cohorts, and further study into any gene-gene interactions or environmental factors that would contribute to the differences in MAF or LD at the rs225014 locus is warranted.

Previous studies have shown an association between Thr92AlaD2 and type 2 diabetes in Brazilians (36), Caucasians (3), and Pima Indians (37) but not in the Danish (38) or Amish (39). However, these studies were performed in younger subjects with an average age in the 20s (37) to 40s (3, 36, 38, 39). In our biracial older population, we found no association with diabetes or BMI. It is possible that the association was attenuated in these older participants owing to the increased prevalence of type 2 diabetes (4.1% in Americans aged 20 to 44 vs 25.9% in those aged ≥65 years) (40). Longitudinal follow-up of populations in which the association is positive in younger adults would aid in this distinction.

These studies had several limitations. That the primary and secondary population studies had different availability of incident outcome data and used populations with differing basal characteristics is important; thus, these results should be interpreted with caution. Further studies with consistent methods performed in large, racially diverse patient populations are needed to replicate these findings. Also, that the regional LD plots for AA and EA cohorts differed markedly could indicate that the Thr92AlaD2 locus is in LD with a SNP (or SNPs) that might be responsible for the observed association. Thus, further studies are needed to define the mechanistic contribution of the two SNPs at a cellular level. Limited numbers of human brain samples were available for transcriptional studies; thus, microarray analysis could not provide statistically definitive results. Future evaluation of more tissue samples by microarray or other technique could be warranted to explore genotype–phenotype associations.

Conclusion

Our results have shown that in these large, well-characterized population studies, the Thr92AlaD2 polymorphism is associated with development of AD in AAs but not EAs. This, in addition to concurrent transcriptional evidence, supports the hypothesis that Thr92AlaD2 is a risk factor for neurodegenerative disease. The rs225014 MAF was significantly greater in AA than in EA participants and perhaps represents one genetic factor contributing to the racial discrepancy in incident AD. It will be important to use racially diverse populations in future trials assessing the rs225014 locus because inheritance patterns vary by race, possibly resulting in disease risk stratification, as demonstrated in these studies.

Supplementary Material

Supplemental Data

Acknowledgments

We thank the older men and women throughout Chicago participating in the CHAP, the older men and women across northeastern Illinois participating in the MAP, and the nuns, priests, and brothers participating in the ROS.

Financial Support: The present study was supported by National Institute on Aging grants P30AG10161, R01AG15819, R01AG17917, and R01AG30146, and the National Institute of Diabetes and Digestive and Kidney Diseases grant R01DK65055. The HRS is supported by National Institute on Aging grants U01AG009740, RC2AG036495, and RC4AG039029 and was conducted by the University of Michigan. The HRS data were obtained from the database of Genotypes and Phenotypes (accession no. phs000428.v1.p1).

Author Contributions: E.A.M. prepared samples for microarray, analyzed microarray data, interpreted population and microarray data, drafted and edited the manuscript. K.B.R. performed

statistical analyses, generated population data and generated tables, and edited the manuscript. D.A.E. provided access to and interpreted the population data, and edited the manuscript. S.J., L.C., and R.P.P. edited the manuscript. D.A.B. provided access to and interpreted the population data and edited the manuscript. D.C.M. provided human brain samples. A.C.B. formulated hypotheses, interpreted the population and microarray data, and edited the manuscript.

Current Affiliation: A.C. Bianco's current affiliation is Section of Endocrinology, Diabetes & Metabolism, University of Chicago Medical Center, Chicago, Illinois 60637.

Disclosure Summary: The authors have nothing to disclose.

Glossary

Abbreviations:

Aβ	amyloid-beta
AD	Alzheimer disease
Ala	alanine
APP	amyloid precursor protein
BMI	body mass index
CHAP	Chicago Health and Aging Project
CI	confidence interval
CIND	cognitive impairment not demented
D2	type II deiodinase
HRS	Health and Retirement Study
IRB	institutional review board
LD	linkage disequilibrium
MAF	minor-allele frequency
MAP	Rush Memory and Aging Project
MCI	mild cognitive impairment
MMSE	Mini-Mental State Examination
OR	odds ratio
ROS	Religious Orders Study
SNP	single nucleotide polymorphism

T3	triiodothyronine
T4	thyroxine
Thr	threonine

References

1. Gereben B, Zavacki AM, Ribich S, Kim BW, Huang SA, Simonides WS, Zeöld A, Bianco AC. Cellular and molecular basis of deiodinase-regulated thyroid hormone signaling. *Endocr Rev*. 2008;29(7):898–938. [PMCID: PMC2647704] [PubMed: 18815314]

2. Peeters RP, van Toor H, Klootwijk W, de Rijke YB, Kuiper GG, Uitterlinden AG, Visser TJ. Polymorphisms in thyroid hormone pathway genes are associated with plasma TSH and iodothyronine levels in healthy subjects. *J Clin Endocrinol Metab*. 2003;88(6):2880–2888. [PubMed: 12788902]

3. Mentuccia D, Proietti-Pannunzi L, Tanner K, Bacci V, Pollin TI, Poehlman ET, Shuldiner AR, Celi FS. Association between a novel variant of the human type 2 deiodinase gene Thr92Ala and insulin resistance: evidence of interaction with the Trp64Arg variant of the beta-3-adrenergic receptor. *Diabetes*. 2002;51(3):880–883. [PubMed: 11872697]

4. Dentice M, Bandyopadhyay A, Gereben B, Callebaut I, Christoffolete MA, Kim BW, Nissim S, Mornon JP, Zavacki AM, Zeöld A, Capelo LP, Curcio-Morelli C, Ribeiro R, Harney JW, Tabin CJ, Bianco AC. The Hedgehog-inducible ubiquitin ligase subunit WSB-1 modulates thyroid hormone activation and PTHrP secretion in the developing growth plate. *Nat Cell Biol*. 2005;7(7):698–705. [PMCID: PMC1761694] [PubMed: 15965468]

5. McAninch EA, Jo S, Preite NZ, Farkas E, Mohácsik P, Fekete C, Egri P, Gereben B, Li Y, Deng Y, Patti ME, Zevenbergen C, Peeters RP, Mash DC, Bianco AC. Prevalent polymorphism in thyroid hormone-activating enzyme leaves a genetic fingerprint that underlies associated clinical syndromes. *J Clin Endocrinol Metab*. 2015;100(3):920–933. [PMCID: PMC4333048] [PubMed: 25569702]

6. de Jong FJ, Peeters RP, den Heijer T, van der Deure WM, Hofman A, Uitterlinden AG, Visser TJ, Breteler MM. The association of polymorphisms in the type 1 and 2 deiodinase genes with circulating thyroid hormone parameters and atrophy of the medial temporal lobe. *J Clin Endocrinol Metab*. 2007;92(2):636–640. [PubMed: 17105838]

7. Wouters HJ, van Loon HC, van der Klauw MM, Elderson MF, Slagter SN, Kobold AM, Kema IP, Links TP, van Vliet-Ostaptchouk JV, Wolffenbuttel BH. No effect of the Thr92Ala polymorphism of deiodinase-2 on thyroid hormone parameters, health-related quality of life, and cognitive functioning in a large population-based cohort study. *Thyroid*. 2017;27(2):147–155. [PubMed: 27786042]

8. Heemstra KA, Hoftijzer HC, van der Deure WM, Peeters RP, Fliers E, Appelhof BC, Wiersinga WM, Corssmit EP, Visser TJ, Smit JW. Thr92Ala polymorphism in the type 2 deiodinase is not associated with T4 dose in athyroid patients or patients with Hashimoto thyroiditis. *Clin Endocrinol (Oxf)*. 2009;71(2):279–283. [PubMed: 19018782]

9. Santoro AB, Vargens DD, Barros Filho MdeC, Bulzico DA, Kowalski LP, Meirelles RM, Paula DP, Neves RR, Pessoa CN, Struchine CJ, Suarez-Kurtz G. Effect of UGT1A1, UGT1A3, DIO1 and DIO2 polymorphisms on L-thyroxine doses required

for TSH suppression in patients with differentiated thyroid cancer. *Br J Clin Pharmacol.* 2014;78(5):1067–1075. [PMCID: PMC4243881] [PubMed: 24910925]

10. Castagna MG, Dentice M, Cantara S, Ambrosio R, Maino F, Porcelli T, Marzocchi C, Garbi C, Pacini F, Salvatore D. DIO2 Thr92Ala reduces deiodinase-2 activity and serum-T3 levels in thyroid-deficient patients. *J Clin Endocrinol Metab.* 2017;102(5):1623–1630. [PubMed: 28324063]

11. Medici M, Chaker L, Peeters RP. A step forward in understanding the relevance of genetic variation in type 2 deiodinase. *J Clin Endocrinol Metab.* 2017;102(5):1775–1778. [PubMed: 28482082]

12. Taylor PN, Peeters R, Dayan CM. Genetic abnormalities in thyroid hormone deiodinases. *Curr Opin Endocrinol Diabetes Obes.* 2015;22(5):402–406. [PubMed: 26192703]

13. Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, DeStafano AL, Bis JC, Beecham GW, Grenier-Boley B, Russo G, Thorton-Wells TA, Jones N, Smith AV, Chouraki V, Thomas C, Ikram MA, Zelenika D, Vardarajan BN, Kamatani Y, Lin CF, Gerrish A, Schmidt H, Kunkle B, Dunstan ML, Ruiz A, Bihoreau MT, Choi SH, Reitz C, Pasquier F, Cruchaga C, Craig D, Amin N, Berr C, Lopez OL, De Jager PL, Deramecourt V, Johnston JA, Evans D, Lovestone S, Letenneur L, Morón FJ, Rubinsztein DC, Eiriksdottir G, Sleegers K, Goate AM, Fiévet N, Huentelman MW, Gill M, Brown K, Kamboh MI, Keller L, Barberger-Gateau P, McGuiness B, Larson EB, Green R, Myers AJ, Dufouil C, Todd S, Wallon D, Love S, Rogaeva E, Gallacher J, St George-Hyslop P, Clarimon J, Lleo A, Bayer A, Tsuang DW, Yu L, Tsolaki M, Bossù P, Spalletta G, Proitsi P, Collinge J, Sorbi S, Sanchez-Garcia F, Fox NC, Hardy J, Deniz Naranjo MC, Bosco P, Clarke R, Brayne C, Galimberti D, Mancuso M, Matthews F, Moebus S, Mecocci P, Del Zompo M, Maier W, Hampel H, Pilotto A, Bullido M, Panza F, Caffarra P, Nacmias B, Gilbert JR, Mayhaus M, Lannefelt L, Hakonarson H, Pichler S, Carrasquillo MM, Ingelsson M, Beekly D, Alvarez V, Zou F, Valladares O, Younkin SG, Coto E, Hamilton-Nelson KL, Gu W, Razquin C, Pastor P, Mateo I, Owen MJ, Faber KM, Jonsson PV, Combarros O, O'Donovan MC, Cantwell LB, Soininen H, Blacker D, Mead S, Mosley TH Jr, Bennett DA, Harris TB, Fratiglioni L, Holmes C, de Bruijn RF, Passmore P, Montine TJ, Bettens K, Rotter JI, Brice A, Morgan K, Foroud TM, Kukull WA, Hannequin D, Powell JF, Nalls MA, Ritchie K, Lunetta KL, Kauwe JS, Boerwinkle E, Riemenschneider M, Boada M, Hiltuenen M, Martin ER, Schmidt R, Rujescu D, Wang LS, Dartigues JF, Mayeux R, Tzourio C, Hofman A, Nöthen MM, Graff C, Psaty BM, Jones L, Haines JL, Holmans PA, Lathrop M, Pericak-Vance MA, Launer LJ, Farrer LA, van Duijn CM, Van Broeckhoven C, Moskvina V, Seshadri S, Williams J, Schellenberg GD, Amouyel P; European Alzheimer's Disease Initiative (EADI); Genetic and Environmental Risk in Alzheimer's Disease; Alzheimer's Disease Genetic Consortium; Cohorts for Heart and Aging Research in Genomic Epidemiology . Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat Genet.* 2013;45(12):1452–1458. [PMCID: PMC3896259] [PubMed: 24162737]

14. Reitz C, Jun G, Naj A, Rajbhandary R, Vardarajan BN, Wang LS, Valladares O, Lin CF, Larson EB, Graff-Radford NR, Evans D, De Jager PL, Crane PK, Buxbaum JD, Murrell JR, Raj T, Ertekin-Taner N, Logue M, Baldwin CT, Green RC, Barnes LL, Cantwell LB, Fallin MD, Go RC, Griffith P, Obisesan TO, Manly JJ, Lunetta KL, Kamboh MI, Lopez OL, Bennett DA, Hendrie H, Hall KS, Goate AM, Byrd GS, Kukull WA, Foroud TM, Haines JL, Farrer LA, Pericak-Vance MA, Schellenberg GD, Mayeux R; Alzheimer Disease Genetics Consortium . Variants in the ATP-binding cassette transporter (ABCA7), apolipoprotein E 4,and the risk of late-onset Alzheimer disease in African Americans. *JAMA.* 2013;309:1483–1492. [PMCID: PMC3667653] [PubMed: 23571587]

15. Jun GR, Chung J, Mez J, Barber R, Beecham GW, Bennett DA, Buxbaum JD, Byrd GS, Carrasquillo MM, Crane PK, Cruchaga C, De Jager P, Ertekin-Taner N, Evans D, Fallin MD, Foroud TM, Friedland RP, Goate AM, Graff-Radford NR, Hendrie H, Hall KS, Hamilton-Nelson KL, Inzelberg R, Kamboh MI, Kauwe JSK, Kukull WA, Kunkle BW, Kuwano R, Larson EB, Logue MW, Manly JJ, Martin ER, Montine TJ, Mukherjee S, Naj A, Reiman EM, Reitz C, Sherva R, St George-Hyslop PH, Thornton T, Younkin SG, Vardarajan BN, Wang LS, Wendlund JR, Winslow AR, Haines J, Mayeux R, Pericak-Vance MA, Schellenberg G, Lunetta KL, Farrer LA; Alzheimer's Disease Genetics Consortium . Transethnic genome-wide scan

identifies novel Alzheimer's disease loci. *Alzheimers Dement.* 2017;13(7):727–738. [PMCID: PMC5496797] [PubMed: 28183528]

16. Hong EP, Park JW. Sample size and statistical power calculation in genetic association studies. *Genomics Inform.* 2012;10(2):117–122. [PMCID: PMC3480678] [PubMed: 23105939]

17. Wilkening S, Chen B, Bermejo JL, Canzian F. Is there still a need for candidate gene approaches in the era of genome-wide association studies? *Genomics.* 2009;93(5):415–419. [PubMed: 19162167]

18. Steenland K, Goldstein FC, Levey A, Wharton W. A meta-analysis of Alzheimer's disease incidence and prevalence comparing African-Americans and Caucasians. *J Alzheimers Dis.* 2016;50(1):71–76. [PMCID: PMC4739787] [PubMed: 26639973]

19. Barnes LL, Leurgans S, Aggarwal NT, Shah RC, Arvanitakis Z, James BD, Buchman AS, Bennett DA, Schneider JA. Mixed pathology is more likely in black than white decedents with Alzheimer dementia. *Neurology.* 2015;85(6):528–534. [PMCID: PMC4540250] [PubMed: 26180136]

20. Bienias JL, Beckett LA, Bennett DA, Wilson RS, Evans DA. Design of the Chicago Health and Aging Project (CHAP). *J Alzheimers Dis.* 2003;5(5):349–355. [PubMed: 14646025]

21. Bennett DA, Schneider JA, Arvanitakis Z, Wilson RS. Overview and findings from the religious orders study. *Curr Alzheimer Res.* 2012;9(6):628–645. [PMCID: PMC3409291] [PubMed: 22471860]

22. Bennett DA, Schneider JA, Buchman AS, Mendes de Leon C, Bienias JL, Wilson RS. The Rush Memory and Aging Project: study design and baseline characteristics of the study cohort. *Neuroepidemiology.* 2005;25(4):163–175. [PubMed: 16103727]

23. Bennett DA, Schneider JA, Buchman AS, Barnes LL, Boyle PA, Wilson RS. Overview and findings from the Rush Memory and Aging Project. *Curr Alzheimer Res.* 2012;9(6):646–663. [PMCID: PMC3439198] [PubMed: 22471867]

24. Rajan KB, Wilson RS, Skarupski KA, Mendes de Leon CF, Evans DA. Gene-behavior interaction of depressive symptoms and the apolipoprotein E varepsilon4 allele on cognitive decline. *Psychosom Med.* 2014;76(2):101–108. [PMCID: PMC4142223] [PubMed: 24434953]

25. Langa KM, Plassman BL, Wallace RB, Herzog AR, Heeringa SG, Ofstedal MB, Burke JR, Fisher GG, Fultz NH, Hurd MD, Potter GG, Rodgers WL, Steffens DC, Weir DR, Willis RJ. The Aging, Demographics, and Memory Study: study design and methods. *Neuroepidemiology.* 2005;25(4):181–191. [PubMed: 16103729]

26. Mailman MD, Feolo M, Jin Y, Kimura M, Tryka K, Bagoutdinov R, Hao L, Kiang A, Paschall J, Phan L, Popova N, Pretel S, Ziyabari L, Lee M, Shao Y, Wang ZY, Sirotkin K, Ward M, Kholodov M, Zbicz K, Beck J, Kimelman M, Shevelev S, Preuss D, Yaschenko E, Graeff A, Ostell J, Sherry ST. The NCBI dbGaP database of genotypes and phenotypes. *Nat Genet.* 2007;39(10):1181–1186. [PMCID: PMC2031016] [PubMed: 17898773]

27. Rajan KB, Wilson RS, Weuve J, Barnes LL, Evans DA. Cognitive impairment 18 years before clinical diagnosis of Alzheimer disease dementia. *Neurology.* 2015;85(10):898–904. [PMCID: PMC4560057] [PubMed: 26109713]

28. Bennett DA, Schneider JA, Aggarwal NT, Arvanitakis Z, Shah RC, Kelly JF, Fox JH, Cochran EJ, Arends D, Treinkman AD, Wilson RS. Decision rules guiding the clinical diagnosis of Alzheimer's disease in two community-based cohort studies compared to standard practice in a clinic-based cohort study. *Neuroepidemiology.* 2006;27(3):169–176. [PubMed: 17035694]

29. Crimmins EM, Kim JK, Langa KM, Weir DR. Assessment of cognition using surveys and neuropsychological

assessment: the Health and Retirement Study and the Aging, Demographics, and Memory Study. *J Gerontol B Psychol Sci Soc Sci.* 2011;66(Suppl 1):i162–i171. [PMCID: PMC3165454] [PubMed: 21743047]

30. Wilson RS, Weir DR, Leurgans SE, Evans DA, Hebert LE, Langa KM, Plassman BL, Small BJ, Bennett DA. Sources of variability in estimates of the prevalence of Alzheimer's disease in the United States. *Alzheimers Dement.* 2011;7(1):74–79. [PMCID: PMC3145367] [PubMed: 21255745]

31. Shulman JM, Chen K, Keenan BT, Chibnik LB, Fleisher A, Thiyyagura P, Roontiva A, McCabe C, Patsopoulos NA, Corneveaux JJ, Yu L, Huentelman MJ, Evans DA, Schneider JA, Reiman EM, De Jager PL, Bennett DA. Genetic susceptibility for Alzheimer disease neuritic plaque pathology. *JAMA Neurol.* 2013;70(9):1150–1157. [PMCID: PMC3773291] [PubMed: 23836404]

32. Sonnega A, Faul JD, Ofstedal MB, Langa KM, Phillips JW, Weir DR. Cohort profile: the Health and Retirement Study (HRS). *Int J Epidemiol.* 2014;43(2):576–585. [PMCID: PMC3997380] [PubMed: 24671021]

33. Johnson AD, Handsaker RE, Pulit SL, Nizzari MM, O'Donnell CJ, de Bakker PI. SNAP: a web-based tool for identification and annotation of proxy SNPs using HapMap. *Bioinformatics.* 2008;24(24):2938–2939. [PMCID: PMC2720775] [PubMed: 18974171]

34. Joshi G, Wang Y. Golgi defects enhance APP amyloidogenic processing in Alzheimer's disease. *BioEssays.* 2015;37(3):240–247. [PMCID: PMC4407201] [PubMed: 25546412]

35. Querfurth HW, LaFerla FM. Alzheimer's disease. *N Engl J Med.* 2010;362(4):329–344. [PubMed: 20107219]

36. Dora JM, Machado WE, Rheinheimer J, Crispim D, Maia AL. Association of the type 2 deiodinase Thr92Ala polymorphism with type 2 diabetes: case-control study and meta-analysis. *Eur J Endocrinol.* 2010;163(3):427–434. [PubMed: 20566590]

37. Nair S, Muller YL, Ortega E, Kobes S, Bogardus C, Baier LJ. Association analyses of variants in the DIO2 gene with early-onset type 2 diabetes mellitus in Pima Indians. *Thyroid.* 2012; 22(1):80–87. [PMCID: PMC3247704] [PubMed: 22142372]

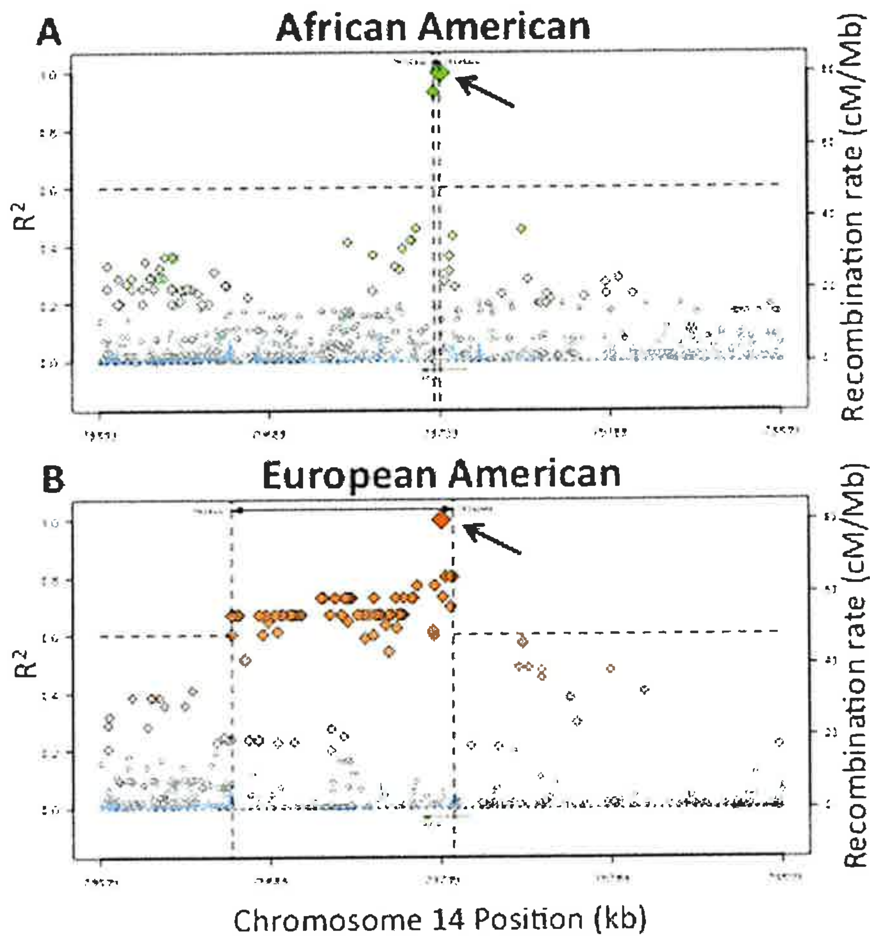
38. Grarup N, Andersen MK, Andreasen CH, Albrechtsen A, Borch-Johnsen K, Jørgensen T, Auwerx J, Schmitz O, Hansen T, Pedersen O. Studies of the common DIO2 Thr92Ala polymorphism and metabolic phenotypes in 7342 Danish white subjects. *J Clin Endocrinol Metab.* 2007;92(1):363–366. [PubMed: 17077128]

39. Mentuccia D, Thomas MJ, Coppotelli G, Reinhart LJ, Mitchell BD, Shuldiner AR, Celi FS. The Thr92Ala deiodinase type 2 (DIO2) variant is not associated with type 2 diabetes or indices of insulin resistance in the old order of Amish. *Thyroid.* 2005;15(1):1223–1227. [PubMed: 16356084]

40. Centers for Disease Control *National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014.* Atlanta, GA: U.S. Department of Health and Human Services; 2014.

31/10/2023,

Figure 1.



Regional LD plots at rs225014 stratified by race. SNPs (diamonds) are indicated by their relative correlation (r^2) with rs225014 (black arrow) plotted against their physical position on chromosome 14. The saturation of the color in the diamond indicates LD with rs225014 according to a scale from $r^2 = 0$ to $r^2 = 1$ based on pairwise r^2 values from the 1000 Genomes Project. The blue line shows the recombination rate across the region. Dashed lines indicate the extent of SNPs within the specified r^2 value of 0.6. The green arrow below shows the location of the known gene in the region (*DIO2*). Plot with SNP data from (A) YRI (Yoruba in Ibadan, Nigeria) population representing AAs and (B) CEU (Utah residents with Northern and Western European ancestry) population representing EAs. Generated using the SNP Annotation and Proxy Search tool (Broad Institute) (33).

Table 1.

Characteristics of Primary and Secondary Cohorts According to Race

Characteristic	Primary			Secondary (HRS)	
	CHAP		ROS/MAP (EAs; n = 1707)		
	AAs (n = 2321)	EAs (n = 1335)		AAs (n = 733)	EAs (n = 6262)
Age at evaluation, y	77.8 ± 6.1	81.2 ± 7.0	86.3 ± 6.8	75.5 ± 7.2	76.5 ± 7.2
Female sex	1450 (62.6)	822 (61.6)	1181 (69.2)	475 (64.8)	3622 (57.8)
BMI, kg/m^2	29.6 ± 6.2	27.4 ± 5.2	27.0 ± 5.2	28.6 ± 6.4	27.5 ± 5.6
Highest education, y	12.0 ± 3.2	14.4 ± 3.2	16.4 ± 3.6	11.6 ± (3.5)	12.9 ± 2.9
Serum total T4, μg/dL	7.5 ± 1.6	7.4 ± 1.7	NA	NA	NA
Diabetes status[a]	772 (21.1)	216 (16.2)	338 (20.2)	284 (38.7)	1707 (27.3)
HbA1c ≥6.5%	457 (28.8)	111 (11.4)	142 (16.3)	NA	NA
Mortality[b]	725 (31.2)	496 (37.2)	1050 (61.5)	121 (16.6)	889 (14.2)
Genotype at rs225014					
Thr/Thr	714 (30.8)	556 (41.7)	726 (42.5)	265 (36.1)	2471 (39.5)
Ala/Thr	1110 (47.8)	604 (45.2)	783 (45.9)	356 (48.6)	2922 (46.7)
Ala/Ala	497 (21.4)	175 (13.1)	198 (11.6)	112 (15.3)	869 (13.9)
Minor allele frequency (%)	45.3	35.7	34.5	41.6	37.3

Data presented as mean ± standard deviation or n (%), unless noted otherwise.

Abbreviations: HbA1c, glycosylated hemoglobin; NA, not available.

[a]Diabetes status was determined by self-report and/or use of diabetes medication.

[b]Mortality was assessed from the Social Security Master Death File and confirmed by the National Death Index through 31 December 2012.

Table 2.

Thr92AlaD2 Polymorphism and ORs for Incident AD or Dementia Relative to No Cognitive Impairment

Model[a]	Primary		Secondary	Meta-Analysis (AD/Dementia)
	CHAP (AD Diagnosis)	ROS/MAP (AD Diagnosis)	HRS (Dementia Diagnosis)	
AAs				
Additive	1.31 (1.02–1.68)	NA	1.33 (0.99–1.78)	1.30 (1.07–1.58)
Dominant	1.85 (1.20–2.85)	NA	1.14 (0.75–1.73)	1.60 (1.15–2.22)
Recessive	1.12 (0.73–1.71)	NA	2.15 (1.26–3.70)	1.33 (0.95–1.87)
EAs				
Additive	0.84 (0.59–1.18)	0.98 (0.83–1.16)	0.95 (0.83–1.09)	0.94 (0.84–1.05)
Dominant	0.89 (0.56–1.40)	0.99 (0.79–1.24)	0.95 (0.78–1.15)	0.94 (0.81–1.09)
Recessive	0.59 (0.26–1.31)	0.95 (0.67–1.35)	0.92 (0.70–1.20)	0.93 (0.42–1.44)

Data presented as OR and 95% CIs.

All ORs were for comparison of participants carrying the minor allele at the rs225014 locus vs those of genotype Thr/Thr (referent).

Abbreviation: NA, not applicable.

[a]The additive statistical model denotes the comparison of [Ala/Thr + 2(Ala/Ala)] vs Thr/Thr; the dominant statistical model denotes the comparison of (Ala/Thr + Ala/Ala) vs Thr/Thr; and the recessive model denotes the comparison of Ala/Ala vs (Ala/Thr + Thr/Thr).

31/10/2023,

Table 3.

Thr92AlaD2 Polymorphism and ORs for Incident MCI or CIND Relative to No Cognitive Impairment

Model	**Primary**		**Secondary HRS (CIND Diagnosis)**	**Meta-Analysis (MCI/CIND)**
	CHAP (MCI Diagnosis)	**ROS/MAP (MCI Diagnosis)**		
AAs				
Additive	1.02 (0.86–1.21)	NA	1.35 (1.09–1.67)	1.27 (1.07–1.52)
Dominant	1.03 (0.79–1.34)	NA	1.35 (0.99–1.84)	1.28 (0.99–1.64)
Recessive	1.04 (0.77–1.39)	NA	1.74 (1.17–2.58)	1.23 (0.97–1.56)
EAs				
Additive	0.88 (0.67–1.12)	0.99 (0.83–1.20)	0.99 (0.91–1.08)	0.98 (0.91–0.95)
Dominant	0.88 (0.62–1.24)	0.90 (0.71–1.15)	0.98 (0.87–1.10)	0.95 (0.86–1.06)
Recessive	0.75 (0.44–1.28)	1.19 (0.82–1.75)	1.00 (0.85–1.18)	1.00 (0.86–1.15)

Data presented as OR and 95% CIs.

All ORs were for comparison of participants carrying the minor allele at the rs225014 locus vs those of genotype Thr/Thr (referent).

Abbreviation: NA, not applicable.

[a]The additive statistical model denotes the comparison of [Ala/Thr + 2(Ala/Ala)] vs Thr/Thr; the dominant statistical model denotes the comparison of (Ala/Thr + Ala/Ala) vs Thr/Thr; and the recessive model denotes the comparison of Ala/Ala vs (Ala/Thr + Thr/Thr).

Table 4.

Participant Characteristics and Thr92AlaD2 Polymorphism Stratified by Race

Variable	**AAs, CHAP**		**EAs, CHAP**		**EAs, ROS/MAP**	
	Ala/Ala +Ala/Thr (n = 1607)	**Thr/Thr (n = 714)**	**Ala/Ala + Ala/Thr (n = 779)**	**Thr/Thr (n = 556)**	**Ala/Ala + Ala/Thr (n = 981)**	**Thr/Thr (n = 726)**
Serum total T4, µg/dL	7.56 ± 1.68	7.48 ± 1.54	7.37 ± 1.59	7.46 ± 1.72	NA	NA
Mortality	483 (30.1)	242 (33.9)	288 (37.0)	208 (37.4)	458 (63.1)	592 (60.4)
BMI, kg/m^2	29.6 ± 6.1	29.4 ± 6.3	27.3 ± 5.2	27.6 ± 5.1	27.0 ± 5.2	27.0 ± 5.2
Diabetes status[a]	536 (33.3)	236 (33.1)	125 (16.1)	91 (16.4)	180 (18.7)	158 (22.2)
HbA1c ≥6.5%	321 (28.8)	136 (28.5)	59 (10.4)	59 (10.4)	86 (17.3)	56 (14.9)

Data presented as mean ± standard deviation or n (%).

Abbreviations: HbA1c, glycosylated hemoglobin; NA, not available.

[a]Diabetes status was determined by self-report and/or the use of diabetes medication.